

01-11-07

10521775 - GAU 1636  
*[Signature]*



Express Mail No.: EV 913 330 314 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Welch et al.

Confirmation No.: 7049

Filed: November 23, 2005

Group Art Unit: 1645

Serial No.: 10/521,775

Examiner: To be Assigned

For: METHODS FOR IDENTIFYING SMALL  
MOLECULES THAT MODULATE  
PREMATURE TRANSLATION  
TERMINATION AND NONSENSE  
MEDIATED mRNA DECAY

Attorney Docket No: 10589-044-999

**INFORMATION DISCLOSURE STATEMENT  
UNDER 37 C.F.R. §§1.56 AND 1.97**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 and §1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Applicants hereby direct the Examiner's attention to references **A01-A34**, **B01-B04** and **C01-C81**, listed on the attached form entitled "List of References Cited by Applicant." Legible copies of references B01-B04 and C01-C81 are submitted herewith.

Copies of references A01-A34 are not submitted herewith because they are U.S. patents, patent publications and pending applications that have been stored in the IFW system of United States Patent and Trademark Office. Pursuant to 37 C.F.R. §1.98 (a)(2)(i) as amended (see Fed. Reg. vol. 69, no. 182, Sept. 21, 2004), the requirement for providing a copy of each U.S. patent or U.S. patent application publication listed in an Information Disclosure Statement in a patent application, regardless of the filing date of the application, is eliminated.

Identification of the listed references is not to be construed an admission of Applicants or Attorneys for Applicants that such references are available as "prior art" against the subject application. Applicants respectfully request that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

Pursuant to 37 C.F.R. §1.97 (b)(3), Applicants estimate that no fee is due in connection with the filing of this Information Disclosure Statement. However, should the Patent Office determine otherwise, please charge the necessary fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: January 9, 2007

*Laura A. Coruzzi* 30,742  
Laura A. Coruzzi (Reg. No.)  
JONES DAY  
222 East 41st Street  
New York, New York 10017  
(212) 326-3939  
By: *2/12 P.M.*  
*Reg. No. 44,412*



LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	ATTY. DOCKET NO.	APPLICATION NO.
	10589-044-999	10/521,775
	APPLICANT Welch et al.	
	FILING DATE November 23, 2005	ART UNIT 1645

**U.S. PATENT DOCUMENTS**

*EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	PAGES, COLUMNS, LINES, WHERE RELEVANT PASSAGES OR RELEVANT FIGURES APPEAR
A01	2003/0232360	12/18/03	Wilusz et al.	
A02	5,015,570	05/14/91	Scangos et al.	
A03	5,510,240	04/23/96	Lam et al.	
A04	5,593,835	01/14/97	Rando et al.	
A05	5,641,627	06/24/97	Moehle	
A06	5,650,316	07/22/97	Aggarwal et al.	
A07	5,663,317	09/02/97	Falkow et al.	
A08	5,666,341	09/09/97	Horibe et al.	
A09	5,667,975	09/16/97	Dykstra et al.	
A10	5,679,566	10/21/97	He et al.	
A11	5,712,096	01/27/98	Stern et al.	
A12	5,716,825	02/10/98	Hancock et al.	
A13	5,807,682	09/15/98	Grossman et al.	
A14	5,840,702	11/24/98	Bedwell	
A15	5,866,341	02/02/99	Spinella et al.	
A16	5,871,923	02/16/99	Moehle	
A17	6,004,749	12/21/99	Giordano et al.	
A18	6,060,240	05/09/00	Kamb et al.	
A19	6,071,700	06/06/00	He et al.	
A20	6,090,912	07/18/00	Lebl et al.	
A21	6,107,029	08/22/00	Giordano	
A22	6,147,344	11/14/00	Annis et al.	
A23	6,207,391	03/27/01	Wu et al.	
A24	6,211,477	04/03/01	Cardott et al.	
A25	6,232,075	05/15/01	Williams	
A26	6,320,040	11/20/01	Cook et al.	
A27	6,329,146	12/11/01	Crooke et al.	

EXAMINER NYI-3914433v3	/Nancy Vogel/	DATE CONSIDERED	11/22/2008
---------------------------	---------------	-----------------	------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.V./

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	PAGES, COLUMNS, LINES, WHERE RELEVANT PASSAGES OR RELEVANT FIGURES APPEAR
	A28	6,355,428	03/12/02	Schroth et al.	
	A29	6,391,542	05/12/02	Anderson et al.	
	A30	6,458,538	10/01/02	Beckman et al.	
	A31	6,503,713	01/07/03	Rana	
	A32	6,503,721	01/07/03	Arenas et al.	
	A33	6,596,481	07/22/03	Rothschild et al.	
	A34	7,026,122	04/11/06	Beckmann et al.	

## FOREIGN PATENT DOCUMENTS

		FOREIGN PATENT DOCUMENT COUNTRY CODE, NUMBER, KIND CODE (IF KNOWN)	DATE	NAME	PAGES, COLUMNS, LINES, WHERE RELEVANT PASSAGES OR RELEVANT FIGURES APPEAR	T
	B01	WO 97/09342	03/13/97	Scriptgen Pharmaceuticals, Inc.		
	B02	WO 99/20797	04/29/99	University of Massachusetts		
	B03	WO 01/44516	06/21/01	Tularik, Inc. PTC Therapeutics, Inc.		
	B04	WO 04/010106	01/29/04	PTC Therapeutics, Inc.		

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials	(Include name of the author (in CAPITAL LETTERS), Title, Date, Pertinent Pages, Etc.)					T
C01	ABOUL-ELA et al., "The structure of the human immunodeficiency virus type-1 TAR RNA reveals principles of RNA recognition by Tat protein." <i>J. Mol. Biol.</i> 1995; 253:313-332.					
C02	AGGARWAL et al., "Triple helix-forming oligodeoxyribonucleotides targeted to the human tumor necrosis factor, TNF, gene inhibit TNF production and block the TNF-dependent growth of human glioblastoma tumor cells." <i>Cancer Res.</i> 1996; 56:5156-5164					
C03	ANDREUTTI-ZAUGG, C. ET AL., "Inhibition of nonsense-mediated messenger RNA decay in clinical samples facilitates detection of human MSH2 mutations with an in vivo fusion protein assay and conventional techniques," <i>Cancer Research</i> 1997; 57(15): 3288-3293.					
C04	BAKHEET et al., "ARED: human AU-rich element-containing mRNA database reveals an unexpectedly diverse functional repertoire of encoded proteins." <i>Nucleic Acids Res.</i> 2001; 29:246-254					
C05	BARTON-DAVIS ET AL., "Animoglycoside antibiotics restore dystrophin function to skeletal muscles of <i>mdx</i> mice" <i>Journal of Clinical Investigation</i> 1999 Aug; 104(4): 375-381					
C06	BATEMAN J.F. ET AL., "Reliable and sensitive detection of premature termination mutations using a protein truncation test designed to overcome problems of nonsense-mediated mRNA instability." <i>Human Mutation</i> 1999; 13(4): 311-317					
C07	BAYER, "Towards The Chemical Synthesis of Proteins." <i>Angew. Chem.</i> 1991; 30:113-129.					
C08	BEAL & DERVAN, "Second structural motif for recognition of DNA by oligonucleotide-directed triple-helix formation." <i>Science</i> 1991; 251(4999):1360-1363					
C09	BEDWELL ET AL., "Suppression of a CFTR premature stop mutation in a bronchial epithelial cell line." <i>Nature Medicine</i> 1997 Nov; 3(11): 1280-1284					
C10	BLACKWELL ET AL., "A one-bead, one-stock solution approach to chemical genetics: part 1." <i>Chem &amp; Bio.</i> 2001; 8:1167-1182.					
C11	BURBAUM J.J. & SIGA, N.H. ET AL., "New technologies for high-throughput screening," <i>Curr. Opin. in Chem. Bio.</i> ; 72-78					

EXAMINER NYI-3914433v3	/Nancy Vogel/	DATE CONSIDERED	11/22/2008
---------------------------	---------------	-----------------	------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.V./

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials	(Include name of the author (in CAPITAL LETTERS), Title, Date, Pertinent Pages, Etc.)	T
C12	BUZINA, A. & SHULMAN, M.J., "Infrequent Translation of a Nonsense Codon is sufficient to decrease mRNA Level." <i>Molecular Biology of the Cell</i> 1999 Mar; 10: 515-524	
C13	CARTER ET AL., "A Regulatory mechanism that detects premature nonsense codons in T-cell receptor transcripts in vivo is reversed by protein synthesis inhibitors in vitro" <i>J. Biol. Chem.</i> 1996; 270(48): 28995-29003	
C14	CARTER ET AL., "A splicing-dependent regulatory mechanism that detects translation signals." <i>The EMBO Journal</i> 1996; 15(21): 5965-5975	
C15	CHASTAIN & TINOCO, "Structural elements in RNA." <i>Prog. Nucleic Acid Res. Mol. Bio.</i> 1991; 41:131-177.	
C16	CHOW & BOGDAN, "A structural basis for RNA-ligand interactions." <i>Chem. Rev.</i> 1997; 97:1489-1514.	
C17	CHURCHER et al., "High affinity binding of TAR RNA by the human immunodeficiency virus type-1 tat protein requires base-pairs in the RNA stem and amino acid residues flanking the basic region" <i>J. Mol. Biol.</i> 1993; 230:90-110.	
C18	CLEMONS ET AL., "A one-bead, one-stock solution approach to chemical genetics: part 2." <i>Chem &amp; Bio.</i> 2001; 8:1183-1195	
C19	CORDINGLEY et al., "Sequence-Specific Interaction of Tat Protein and Tat Peptides with the Transactivation-Responsive Sequence Element of Human Immunodeficiency Virus Type 1 in vitro." <i>Proc. Natl. Acad. Sci. USA</i> 1990; 87:8985-8989.	
C20	CULBERTSON, M.R., "Unforeseen consequences for gene expression, inherited genetic disorder and cancer." <i>TIG Nature Medicine</i> 1999 Feb; 15(2): 74-80	
C21	CUNDLIFFE ET AL., "How antibiotic-producing organisms avoid suicide." <i>Ann. Rev. Microbiol.</i> 1989; 43:207-233	
C22	CUNDLIFFE ET AL., "The Ribosome: Structure, Function, & Evolution." Schlessinger et al., eds. American Society for Microbiology, Washington D.C. 1990; pp. 409-417	
C23	DARLING, T. N. ET AL., "Cycloheximide facilitates the identification of aberrant transcripts resulting from a novel splice-site mutation in COL17A1 in a patient with generalized atrophic benign epidermolysis bullosa." <i>J. of Invest. Dermatol.</i> 1998 Feb; 110(2): 165-169	
C24	DARLING, T.N. ET AL., "Premature Termination Codons are present on both alleles of the Bullous Pemphigoid Antigen 2/Type XVIII Collagen Gene in Five Austrian Families with Generalized Atrophic Benign Epidermolysis Bullosa." <i>J. Invest. Dermatol.</i> 1997; Apr; 108(4): 463-468	
C25	DINMAN, J.D. ET AL., "Translating old drugs into new treatments: ribosomal frameshifting as a target for antiviral agents." <i>Tibtech (reviews)</i> 1998 Apr; 16:190-196	
C26	FELBER & PAVLAKIS, "A quantitative bioassay for HIV-1 based on trans-activation." <i>Science</i> 1988; 239:184-187.	
C27	FERNANDES, "Technological advances in high-throughput screening." <i>Curr Opin Chem Biol.</i> 1998; 2:597-603	
C28	FRANKEL A. D. & PABO, "Cellular uptake of the tat protein from human immunodeficiency virus." <i>Cell</i> 1998; 55:1189-1194.	
C29	GARVIN, A.M., "A complete protein truncation test for BRCA1 and BRCA2." <i>European Journal of Human Genetics.</i> 1998 May; 6(3): 226-234	
C30	GOTTESFELD et al. "Regulation of gene expression by small molecules. <i>Nature</i> 1997; 387(6629):202-205.	
C31	GOTTESFELD et al., "Chemical Approaches to Control Gene Expression." <i>Gene Expr</i> 2000; 9:77-91	
C32	HAMY et al., "A new class of HIV-1 Tat antagonist acting through Tat-TAR inhibition." <i>Biochem</i> 1998; 37(15):5086-5095.	
C33	HAMY et al., "An inhibitor of the Tat/TAR RNA interaction that effectively suppresses HIV-1 replication." <i>Proc. Natl. Acad. Sci. USA</i> 94:3548-3553.	
C34	HARNDEN et al., "Thiazolinone Analogues of Indomycin with antiviral and antibacterial activity." <i>J. of Med. Chem.</i> 1978; 21:82-87	
C35	HELENE et al., "Control of gene expression by triple helix-forming oligonucleotides. The antigene strategy." <i>Ann N Y Acad Sci</i> 1992; 660:27-36.	
C36	HENTZE, M.W. & KULOZIK, A.E. "A Perfect Message: RNA Surveillance and Nonsense-Mediated Decay" <i>Cell</i> 1999 Feb; 96: 307-310	
C37	HO et al., "Specific inhibition of formation of transcription complexes by a calicheamicin oligosaccharide: a paradigm for the development of transcriptional antagonists." <i>Proc Natl Acad Sci USA</i> 1994; 91(20):9203-9207.	

EXAMINER NYI-3914433v3	/Nancy Vogel/	DATE CONSIDERED	11/22/2008
---------------------------	---------------	-----------------	------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.V./

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials	(Include name of the author (in CAPITAL LETTERS), Title, Date, Pertinent Pages, Etc.)	T
C38	HOWARD ET AL., "Aminoglycoside antibiotics restore CFTR function by overcoming premature stop mutations." <i>Nature Medicine</i> 1996 Apr; 2(4): 467-46	
C39	HUQ et al., "Controlling human immunodeficiency virus type 1 gene expression by unnatural peptides." <i>Biochem.</i> 1999; 38:5172-5177.	
C40	HUTCHIN ET AL., "A molecular basis for human hypersensitivity to aminoglycoside antibiotics" <i>Nucl. Acids Res</i> 1993; 21(18):4174-4179	
C41	HWANG et al., "Inhibition of gene expression in human cells through small molecule-RNA interactions." <i>Proc. Natl. Acad. Sci. USA</i> 1999; 96(23):12977-13002.	
C42	JACKSON, R.J. & HUNT, T. "Preparation and Use of Nuclease-Treated Rabbit Reticulocyte Lysates for the Translation of Eukaryotic Messenger RNA." <i>Methods in Enzymology</i> 1983; 96: 50-75.	
C43	JAKOBOWITS et al., "A discrete element 3' of human immunodeficiency virus 1 (HIV-1) and HIV-2 mRNA initiation sites mediates transcriptional activation by an HIV trans activator." <i>Mol. Cell. Bio.</i> 1988; 8:2555-2561.	
C44	JHAVERI et al., "In Vitro Selection of RNA Aptamers to a Protein Target by Filter Immobilization" <i>Curr. Prot. in Molec. Bio.</i> 2000; 24.3.1-24.3.25	
C45	JONES & PETERLIN, "Control of RNA initiation and elongation at the HIV-1 promoter." <i>Annu Rev Biochem</i> 1994; 63:717-743.	
C46	KURUVILLA ET AL., "Dissecting glucose signalling with diversity-oriented synthesis and small-molecule microarrays." <i>Nature</i> 2002; 416:653-657	
C47	LI, S. & WILKINSON, F., "Nonsense Surveillance in Lymphocytes?" <i>Immunity</i> 1998 Feb; 8: 135-141	
C48	LIU et al., "Sequence-selective carbohydrate-DNA interaction: Dimeric and monomeric forms of the calicheamicin oligosaccharide interfere with transcription factor function." <i>Proc Natl Acad Sci USA</i> 1996; 93(2):940-944.	
C49	MAHER et al., "Oligonucleotide-directed DNA triple-helix formation: an approach to artificial repressors?" <i>Antisense Res Dev</i> 1991; 1(3):277-281.	
C50	MAZUMDER et al., "Inhibition of the Human Immunodeficiency Virus Type 1 Integrase by Guanosine Quartet Structures." <i>Biochem.</i> 1996; 35:13762-13771	
C51	MEI et al., "Inhibitors of protein-RNA complexation that target the RNA: specific recognition of human immunodeficiency virus type 1 TAR RNA by small organic molecules." <i>Biochem.</i> 1998; 37(40):14204-14212.	
C52	MEI et al., "Discovery of selective, small-molecule inhibitors of RNA complexes--I. The Tat protein/TAR RNA complexes required for HIV-1 transcription." <i>Bioorg. Med. Chem.</i> 1997; 5:1173-1184.	
C53	MILLER, "Development of antisense and antigenic oligonucleotide analogs." <i>Prog. Nucleic Acid Res. Mol. Bio.</i> 1996; 52:261-291.	
C54	MILLIGAN et al., "Oligoribonucleotide synthesis using T7 RNA polymerase and synthetic DNA templates." <i>Nucleic Acids Res.</i> 1987;15:8783-8798.	
C55	MISIURA et al., "Biotinyl and phosphotyrosinyl phosphoramidite derivatives useful in the incorporation of multiple reporter groups on synthetic oligonucleotides." <i>Nucleic Acids Res.</i> 1990; 18:4345-4354.	
C56	MULLER et al., "Interaction of fluorescently labeled dideoxynucleotides with HIV-1 reverse transcriptase." <i>Biochem.</i> 1991; 30:3709-3715.	
C57	NEEDELS et al., "Generation and screening of an oligonucleotide-encoded synthetic peptide library", <i>Proc. Natl. Acad. Sci. USA</i> 1993; 90:10700-10704.	
C58	NEENHOLD & RANA, "Major groove opening at the HIV-1 Tat binding site of TAR RNA evidenced by a rhodium probe." <i>Biochem.</i> 1995; 34:6303-6309.	
C59	NIELSEN, "Applications of peptide nucleic acids." <i>Curr. Opin. Biotechnol.</i> 1999; 10(1):71-75.	
C60	NORDEEN, "Luciferase reporter gene vectors for analysis of promoters and enhancers." <i>Bio Techniques</i> 1998; 6:454-457.	
C61	OHLMEYER et al., "Complex synthetic chemical libraries indexed with molecular tags." <i>Proc. Natl. Acad. Sci. USA</i> 1993; 90(23):10922-10926	
C62	OJWANG et al., "Achieving antisense inhibition by oligodeoxynucleotides containing N7 modified 2'-deoxyguanosine using tumor necrosis factor receptor type 1." <i>METHODS: A Companion to Methods in Enzymology</i> 1999; 18:244-251	
C63	PING et al., "Dynamics of RNA-protein interactions in the HIV-1 Rev-RRE complex visualized by 6-thioguanosine-mediated photocrosslinking" <i>RNA</i> 1997; 3:850-860.	

EXAMINER NYI-3914433v3	/Nancy Vogel/	DATE CONSIDERED	11/22/2008
---------------------------	---------------	-----------------	------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.V./

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials	(Include name of the author (in CAPITAL LETTERS), Title, Date, Pertinent Pages, Etc.)	T
C64	PUGLISI et al., "Conformation of the TAR RNA-arginine complex by NMR spectroscopy." <i>Science</i> 1992; 257:76-80.	
C65	PUROHIT ET AL., "Interactions of a small RNA with antibiotic and RNA ligands of the 30S subunit" <i>Nature</i> 1994; 370(6491):659-662	
C66	RANDO et al., "Biologic activity of guanosine quartet forming oligonucleotides" in "Applied Antisense Oligonucleotide Technology" Stein and Krieg, eds, John Wiley and Sons, New York, 1998; pages 335-352	
C67	RUIZ-ECHEVARRIA ET AL., "Making sense of nonsense in yeast" <i>TIBS</i> 1996 Nov; 21: 433-438	
C68	SCARINGE et al., "Chemical synthesis of biologically active oligoribonucleotides using beta-cyanoethyl protected ribonucleoside phosphoramidites. <i>Nucleic Acids Res</i> 1990; 18:5433-5441.	
C69	SHAH et al., "Incorporation of an artificial protease and nuclease at the HIV-1 Tat binding site of trans-activation responsive RNA." <i>Bioconjugate Chem.</i> 1996; 7:283-289.	
C70	SHAH et al., "Synthesis of uridine phosphoramidite analogs: reagents for site-specific incorporation of photoreactive sites into RNA sequences." <i>Bioconjugate Chem.</i> 1994; 5:508-512.	
C71	STAGE ET AL., "Inhibition of the hammerhead ribozyme by neomycin" <i>RNA</i> 1995; 1(1):95-101	
C72	STERNSON ET AL., "Split-Pool Synthesis of 1,3-Dioxanes Leading to Arrayed Stock Solutions of Single Compounds Sufficient for Multiple Phenotypic and Protein-Binding Assays." <i>J. Am. Chem. Soc.</i> 2001; 123:1740-1747	
C73	STILL, "Discovery of sequence-selective peptide binding by synthetic receptors using encoded combinatorial libraries." <i>Accounts of Chem. Res.</i> 1996; 29:(3) 155-163.	
C74	VON AHSEN ET AL., "Antibiotic inhibition of group I ribozyme function." <i>Nature (London)</i> 1991; 353(6342):368-370	
C75	WANG & RANA, "RNA conformation in the Tat-TAR complex determined by site-specific photo-cross-linking." <i>Biochem</i> 1996; 35:6491-6499.	
C76	WEEKS & CROTHERS, "Major groove accessibility of RNA." <i>Science</i> 1993; 261(5128):1574-1577.	
C77	WHITE et al., "Recognition of the four Watson-Crick base pairs in the DNA minor groove by synthetic ligands." <i>Nature</i> 1998; 391(6666):468-471.	
C78	WOODCOCK ET AL., "Interaction of antibiotics with A- and P-site-specific bases in 16S ribosomal RNA" <i>EMBO J.</i> 1991; 10:3099-3103	
C79	XAVIER et al., "RNA as a drug target: methods for biophysical characterization and screening." <i>Trends Biotechnol</i> 2001; 18:349-356	
C80	XIAN et al., "DNA-protein binding assays from single sea urchin egg: a high sensitivity capillary electrophoresis method." <i>Proc. Natl. Acad. Sci.</i> 1996; 93:86-90	
C81	ZAPP ET AL. "Small molecules that selectively block RNA binding of HIV-1 Rev protein inhibit Rev function and viral production" <i>Cell</i> 1993; 74(6):969-978	

EXAMINER  
NYI-3914433v3

/Nancy Vogel/

DATE CONSIDERED

11/22/2008

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.V./